II. REMARKS

Reconsideration of this application, in view of the changes made and arguments presented herein, is respectfully requested.

A. Status of the Claims

Claims 1, 4, 5, 7, 8, 10-18 and 20 are pending. Claims 1, 7, 17 and 20 have been amended without prejudice to more particularly point out and distinctly claim the invention. The subject matter of claims 3 and 6 has been incorporated into claim 1, and claims 2, 3 and 6 have been cancelled without prejudice. Claim 7 has been amended to depend from claim 1 rather than claim 6 which has been canceled by virtue of the present amendment. The subject matter of claim 19 has been incorporated into claim 17, therefore claim 19 has been canceled.

It is respectfully submitted that no new matter has been added by virtue of this amendment. Additionally, Applicants respectfully submit the amendments to the claims do not raise any issues that would require further consideration and/or search, because all the subject matter of the additions to the independent claims was previously considered by the Examiner.

Further, the changes being made to the claims and arguments presented herein are directed to one particular aspect of the invention, and are not meant to restrict applicants' ability to seek coverage for additional/different aspects of the invention in a continuation application.

B. Examiner's Comments Regarding Information Disclosure Statement

The Examiner contacted the undersigned and indicated that the references cited in the Information Disclosure Statement were missing. Accordingly, Applicants submit herewith copies of the references cited in sheets 1-2 of Form PTO-1449 accompanying the Information Disclosure Statement submitted on April 13, 2007.

C. Statement of Substance of Interview

In accordance with the provisions of 37 CFR 1.133, Applicants herein make of record the substance of the telephonic interview conducted on February 26, 2008, between Applicants' attorneys, Clifford M. Davidson and Benjamin DiMarco and Examiner Blessing Fubaru.

During the interview, the claims of the application were discussed in view of the references cited and the rejections made in the Office Action mailed August 28, 2007. It was explained that a distinction of certain preferred aspects of the invention relates to buprenorphine microspheres that are prepared in a manner to achieve a high load of buprenorphine. This is accomplished pursuant to certain examples by utilizing buprenorphine free base and a buffered aqueous solution as seen in Examples 20, 21, 23 and 25 providing a drug load of 81.8, 72, 84.7 and 85 μg of buprenorphine per mg of microsphere, respectively. By way of comparison, Example 18, which was prepared using buprenorphine hydrochloride and phosphate buffer, only achieved a drug load of 36.3 μg buprenorphine per mg of microspheres.

It was proposed to amend claim 17 to include the subject matter of claim 3, thereby requiring buprenorphine free base in the manufacture of the buprenorphine microspheres. It was further proposed amending claim 17 by incorporating the subject matter of claim 6, thereby requiring that the buffered aqueous solution of PVA (used to prepare an emulsion containing microspheres), has a pH from about 6.8 to about 8.0.

It was explained that support for the claimed pH range of about 6.8 to about 8.0 was also found in the originally filed claims. This pH range was incorporated into the specification as paragraph [0029.4] at page 3 of Applicants' previous amendment to the

specification filed on April 13, 2006. Additionally, it was also explained that support for the claimed PLGA inherent viscosity ranges is found in the specification and in the examples.

During the interview, the Examiner inquired as to support for the ranges of first and second specific viscosities of the PLGA's recited in the claims.

Support for the claimed PLGA specific viscosity ranges: (i) between about 0.01 and about 0.31 dL/g, and (ii) between about 0.40 and about 0.88 dL/g is found in claim 9 as originally filed, and was incorporated into the specification as paragraph [0029.6] at page 3 of Applicants' previous amendment to the specification filed on April 13, 2006.

In addition, the two different PLGA's used in each of Examples 20 and 21 had specific viscosities of 0.16 dL/g and 0.64 dL/g. The two different PLGA's used in each of Examples 23 and 24 had specific viscosities of 0.20 dL/g and 0.66 dL/g. Example 1 and others use a PLGA having a specific viscosity of 0.7dL/g. Examples 3 and 6 use a PLGA having a specific viscosity of 0.67 dL/g. As discussed during the Examiner interview of February 26, 2008, when comparing "apples to apples", as can be accomplished when comparing Examples 18 and 20, i.e., where the specific viscosities of both the first and second PLGA's were identical, an improvement in drug load was seen when substituting buprenorphine hydrochloride in Example 18 with buprenorphine free base in Example 20. As discussed during the interview, Example 18 (using buprenorphine hydrochloride in a pH 7.5 phosphate buffer) only achieved a drug load of 36.3 μg buprenorphine per mg of microsphere. By contrast, Example 20 (utilizing buprenorphine free base) achieved a drug load of 81.8 μg buprenorphine per mg of microsphere. Therefore, it is respectfully submitted that production of high load buprenorphine microspheres can be accomplished by using PLGA's having different specific viscosities.

Finally, during the interview the Examiner inquired about the differences between the amount of 89.5 mg buprenorphine hydrochloride (equivalent to 82.9 mg of

buprenorphine base)[1], in Example 18 and the amount of 89.3 mg buprenorphine in Example 20. Applicants respectfully submit that this minor difference in the amounts of buprenorphine does not account for the difference in drug load between Examples 18 and 20. Instead, the difference is accomplished from using the free base form of buprenorphine rather than the hydrochloride salt form.

Applicants respectfully request that the substance of the interview be made of record.

D. 35 U.S.C. §103 Rejections

In the Office Action, the Examiner maintained the rejection of claims 1-8 and 10-20 under 35 U.S.C. § 103(a) as being obvious over United States Patent No. 5,000,886 to Lawter et al., ("Lawter"), in view of United States Patent No. 6,716,449 to Oshlack et al., ("Oshlack") or Japan Patent Application No. JP 403103732A to Hille et al., ("Hille").

In response to Applicants' arguments, the Examiner took the position that "Lawter does not teach away from the invention because Lawter specifically teaches that blends of polymers can be used (column 4, lines 59 and 60)" and that "Oshlack is relied upon for teaching formulating buprenorphine with polyvinyl alcohol. Therefore, one would arrive at the claimed invention by using the teaching of Lawter that blends of polymers can be used when formulating active agents such as buprenorphine and the examples guides the artisan to use specific PLGA's having the specific viscosities."

The Examiner also took the position that while the embodiments exemplified do not contain buprenorphine, any of the drugs listed can be prepared by the process of Lawter. The Examiner concluded that it is "prima facie obvious to combine two compositions each of which is taught by the prior art to be used for the same purpose, in

[1] This was calculated using information contained in the Package Insert for the product Bruprenex®, which contains buprenorphine. Therein, it states that 0.324 mg buprenorphine hydrochloride is equivalent to 0.3 mg buprenorphine base). See Exhibit A attached herewith to this Amendment (Buprenex® Package Insert).

order to form a third composition to be used for the very same purpose . . . [T]he idea of combining them flows logically from their having been individually taught by the prior art", citing In re Kerkhoven, 626 F.2d 846, 850, 205 U.S.P.Q. 1069, 1072 (C.C.P.A. 1980). The Examiner further stated that "in this case, a third composition that contains PLGA having different viscosities and containing buprenorphine is rendered obvious with expectation of success that the compositions can be successfully formulated."

This rejection is respectfully traversed. Claim 1 as currently amended recites:

1. A pharmaceutical formulation for extended release of buprenorphine from microspheres, said formulation made by steps comprising: admixing PLGA having a first specific viscosity between about 0.01 and about 0.31 dL/g with PLGA having a second specific viscosity between about 0.40 and about 0.88 dL/g to form a PLGA mixture; admixing the PLGA mixture with a halogenated organic solvent to form a PLGA-halogenated organic solvent mixture; admixing the PLGA-halogenated organic solvent mixture with buprenorphine free base to form a buprenorphine-PLGA-halogenated organic solvent mixture; admixing a buffered aqueous solution of PVA having a pH of from about 6.8 to about 8.0 with the buprenorphine-PLGA-halogenated organic solvent mixture to form an emulsion containing microspheres comprising a drug consisting of buprenorphine; recovering at least one of said microspheres from the emulsion.

Claim 17 as currently amended recites:

17. (Currently Amended) A process for making a pharmaceutical formulation for extended release of buprenorphine from microspheres, said process comprising: admixing PLGA having a first specific viscosity between about 0.01 and about 0.31 dL/g with PLGA having a second specific viscosity between about 0.40 and about 0.88 dL/g to form a PLGA mixture; admixing the PLGA mixture with a halogenated organic solvent to form a PLGA-halogenated organic solvent mixture; admixing the PLGA-halogenated organic solvent mixture with buprenorphine free base to form a buprenorphine-PLGA-halogenated organic solvent mixture; admixing a buffered aqueous solution of PVA having a pH from about 6.8 to about 8.0 with the buprenorphine-PLGA-halogenated organic solvent mixture to form an emulsion comprising microspheres, said microspheres comprising buprenorphine; recovering at least one of said microspheres from the emulsion.

Claim 20 as currently amended recites:

20. A method of treating a mammal in which treatment with buprenorphine is indicated, said method comprising the step of administering to the mammal a pharmaceutically effective quantity of buprenorphine-containing microspheres prepared by a process comprising: admixing PLGA between about 0.01 and about 0.31 dL/g having a first specific viscosity with PLGA having a second specific viscosity between about 0.40 and about 0.88 dL/g to form a PLGA mixture; admixing the PLGA mixture with a halogenated organic solvent to form a PLGA-halogenated organic solvent mixture; admixing the PLGA-halogenated organic solvent mixture with buprenorphine free base to form a buprenorphine-PLGA-halogenated organic solvent mixture; admixing a buffered aqueous solution of PVA having a pH from about 6.8 to about 8.0 with the buprenorphine-PLGA-halogenated organic solvent mixture to form an emulsion containing microspheres comprising buprenorphine; recovering at least one of said microspheres from the emulsion.

The Lawter Patent

As explained in the preceding paragraphs, the product described in claim 1 and the method of claim 20 provide a high load buprenorphine microsphere product. Lawter does not distinguish the use of buprenorphine free base from buprenorphine hydrochloride and does not suggest the use of a buffered aqueous solution of PVA having a pH of from about 6.8 to about 8.0. It is respectfully submitted that following the teaching of Lawter one of ordinary skill in the art would not arrive at a high load microsphere formulation, without the benefit of hindsight provided only by the present application. By contrast, the examples of the instant application demonstrate that only through selection of the specific limitations of the independent claims as presently amended, that one arrives at a high load product.

It is respectfully submitted that Lawter does not provide any motivation to pick buprenorphine free base out of a long list of possible actives, then further pick two separately considered PLGA's, and then admix that combination together in the specified fashion, i.e., with a buffered aqueous solution of PVA having a pH from about 6.8 to

about 8.0, to arrive at the claimed invention, which provides a high load buprenorphine microsphere pharmaceutical formulation.

Moreover, Lawter mentions buprenorphine in a long list of active agents. Nothing in Lawter suggests mixing buprenorphine free base and two PLGA's of different specific viscosities in the specific manner set forth in the independent claims, which is respectfully submitted to provide an unexpected result. In fact, Lawter only describes the use of only one PLGA having one specific viscosity, and not a mixture of different materials, in its disclosure. It is respectfully submitted that there is no basis to assert that Lawter hints or suggests that microcapsules having buprenorphine as the active agent should utilize any particular PLGA specific viscosity, let alone the combination of two PLGA's presently claimed. Certainly, there is no general discussion in Lawter of any preferred PLGA's having preferred specific viscosities; and the examples in Lawter upon which the Examiner relies are directed to completely different active agents having completely different physical/chemical properties. The fact that Lawter exemplifies two products each of which uses a different PLGA is respectfully submitted to only suggest that different PLGA's can be used in Lawter, not that a combination of two PLGA's should be used.

The Examiner's position that "a third composition that contains PLGA having different viscosities and containing buprenorphine is rendered obvious with expectation of success that the compositions can be successfully formulated" (Page 7, second complete paragraph of the Office Action) flies in the face of the Examiner's own admission of the unpredictable nature of the pharmaceutical art and the lack of any suggestion in Lawter to obtain a high load buprenorphine microsphere product by selecting the buprenorphine free base form, and admixing a buffered aqueous solution of PVA having a pH of from about 6.8 to about 8.0.

The Oshlack Patent

Oshlack does not teach one of ordinary skill in the art to obtain the predicted results as demonstrated by the examples set forth in the specification of the instant application. Oshlack is relied upon for teaching formulating buprenorphine with PVA.

Oshlack fails to teach one of ordinary skill in the art that a high load buprenorphine microsphere product can be obtained by selecting the buprenorphine free base form, and admixing a the two PLGA's/buprenorphine base mixture with a buffered aqueous solution of PVA having a pH of from about 6.8 to about 8.0. Accordingly, it is respectfully submitted that Oshlack does not overcome the deficiencies of Lawter with respect to the independent claims, as currently amended.

With respect to independent product claim 1, it is further respectfully submitted that Oshlack only describes a combination product of buprenorphine and naltrexone (see Example 20 of Oshlack). This possibility is eliminated in claim 1, which has now been limited to microspheres including a drug *consisting of* buprenorphine.

It is respectfully submitted that following the teaching of Lawter in combination with Oshlack, one of ordinary skill in the art would still not arrive at a high load buprenorphine microsphere formulation, without the benefit of hindsight obtained only through the knowledge imparted by the present application.

The Hille Reference

The teaching of Hille also fails to provide a basis for overcoming the deficiencies of Lawter taken alone, or Lawter in view of Oshlack because Hille also fails to teach one of ordinary skill in the art to obtain a high load buprenorphine microsphere product by selecting the buprenorphine free base form, and using a buffered aqueous solution of PVA having a pH of from about 6.8 to about 8.0.

Accordingly, in view of the above arguments and amendments to the claims, it is respectfully requested that the Examiner's rejection under 35 U.S.C. § 103(a) of independent claims 1, 17 and 20 and the claims dependent there from be withdrawn.

III. Conclusion

In view of the actions taken, it is respectfully submitted that the present application is now in condition for allowance. An early and favorable action on the merits is earnestly solicited. According to currently recommended Patent Office policy the Examiner is specifically authorized to contact the undersigned in the event that a telephone interview will advance the prosecution of this application. A request for a three-month extension of time to reply to the Office Action along with the requisite fee is enclosed.

Respectfully submitted,

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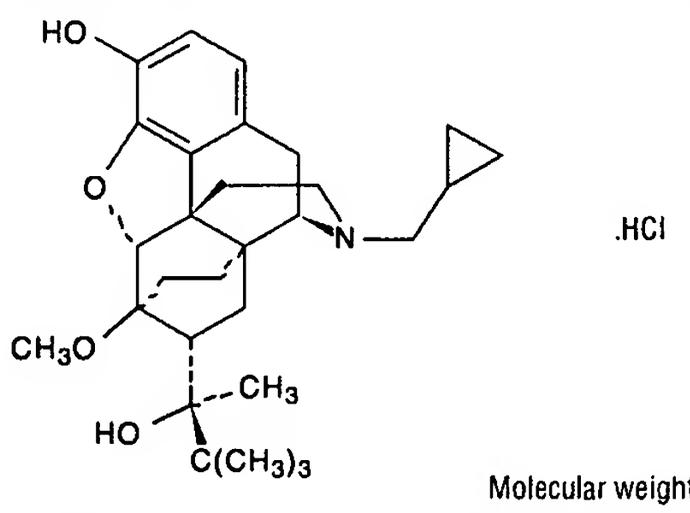
Exhibit A

NDC 12496-0757-1

Buprenex®
(buprenorphine hydrochloride)
Injectable
Rx only

DESCRIPTION: Buprenex (buprenorphine hydrochloride) is a narcotic under the Controlled Substances Act due to its chemical derivation from thebaine. Chemically, it is 17-(cyclopropylmethyl)-α-(1, 1-dimethylethyl)-4, 5-epoxy-18, 19-dihydro-3-hydroxy-6-methoxy-α-methyl-6, 14-ethenomorphinan-7-methanol, hydrochloride [5α, 7α(S)]. Buprenorphine hydrochloride is a white powder, weakly acidic and with limited solubility in water. Buprenex is a clear, sterile, injectable agonist-antagonist analgesic intended for intravenous or intramuscular administration. Each ml of Buprenex contains 0.324 mg buprenorphine hydrochloride (equivalent to 0.3 mg buprenorphine), 50 mg anhydrous dextrose, water for injection and HCl to adjust pH. Buprenorphine hydrochloride has the molecular formula, $C_{29}H_{41}NO_4HCl$, and the following structure:



.HCl

Molecular weight: 504.09

CLINICAL PHARMACOLOGY: Buprenex is a parenteral opioid analgesic with 0.3mg Buprenex being approximately equivalent to 10 mg morphine sulfate in analgesic and respiratory depressant effects in adults. Pharmacological effects occur as soon as 15 minutes after intramuscular injection and persist for 6 hours or longer. Peak pharmacologic effects usually are observed at 1 hour. When used intravenously, the times to onset and peak effect are shortened.

The limits of sensitivity of available analytical methodology precluded demonstration of bioequivalence between intramuscular and intravenous routes of administration. In postoperative adults, pharmacokinetic studies have shown elimination half-lives ranging from 1.2-7.2 hours (mean 2.2 hours) after intravenous administration of 0.3mg of buprenorphine. A single, ten-patient, pharmacokinetic study of doses of 3μg/kg in children (age 5-7 years) showed a high inter-patient variability, but suggests that the clearance of the drug may be higher in children than in adults. This is supported by at least one repeat-dose study in postoperative pain that showed an optimal inter-dose interval of 4-5 hours in pediatric patients as opposed to the recommended 6-8 hours in adults.

Buprenorphine, in common with morphine and other phenolic opioid analgesics, is metabolized by the liver and its clearance is related to hepatic blood flow. Studies in patients anesthetized with 0.5% halothane have shown that this anesthetic decreases hepatic blood flow by about 30%.

Mechanism of Analgesic Action: Buprenex exerts its analgesic effect via high affinity binding to μ subclass opiate receptors in the central nervous system. Although Buprenex may be classified as a partial agonist, under the conditions of recommended use it behaves very much like classical μ agonists such as morphine. One unusual property of Buprenex observed in *in vitro* studies is its very slow rate of dissociation from its receptor. This could account for its longer duration of action than morphine, the unpredictability of its reversal by opioid antagonists, and its low level of manifest physical dependence.

Narcotic Antagonist Activity: Buprenorphine demonstrates narcotic antagonist activity and has been shown to be equipotent with naloxone as an antagonist of morphine in the mouse tail flick test.

Cardiovascular Effects: Buprenex may cause a decrease or, rarely, an increase in pulse rate and blood pressure in some patients.

Effects on Respiration: Under usual conditions of use in adults, both Buprenex and morphine show similar dose-related respiratory depressant effects. At adult therapeutic doses, Buprenex (0.3mg buprenorphine) can decrease respiratory rate in an equivalent manner to an equianalgesic dose of morphine (10mg). (See WARNINGS.)

INDICATIONS AND USAGE: Buprenex is indicated for the relief of moderate to severe pain.

CONTRAINDICATIONS: Buprenex should not be administered to patients who have been shown to be hypersensitive to the drug.

WARNINGS:
Impaired Respiration: As with other potent opioids, clinically significant respiratory depression may occur within the recommended dose range in patients receiving therapeutic doses of buprenorphine. Buprenex should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression). Particular caution is advised if Buprenex is administered to patients taking or recently receiving drugs with CNS/respiratory depressant effects. In patients with the physical and/or pharmacological risk factors above, the dose should be reduced by approximately one-half.

NALOXONE MAY NOT BE EFFECTIVE IN REVERSING THE RESPIRATORY DEPRESSION PRODUCED BY BUPRENEX. THEREFORE, AS WITH OTHER POTENT OPIOIDS, THE PRIMARY MANAGEMENT OF OVERDOSE SHOULD BE THE REESTABLISHMENT OF ADEQUATE VENTILATION WITH MECHANICAL ASSISTANCE OF RESPIRATION, IF REQUIRED.

Interaction with Other Central Nervous System Depressants: Patients receiving Buprenex in the presence of other narcotic analgesics, general anesthetics, antihistamines, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics or other CNS depressants (including alcohol) may exhibit increased CNS depression. When such combined therapy is contemplated, it is particularly important that the dose of one or both agents be reduced.

Head Injury and Increased Intracranial Pressure: Buprenex, like other potent analgesics, may itself elevate cerebrospinal fluid pressure and should be used with caution in head injury, intracranial lesions and other circumstances where cerebrospinal pressure may be increased. Buprenex can produce miosis and changes in the level of consciousness which may interfere with patient evaluation.

Use in Ambulatory Patients: Buprenex may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Therefore, Buprenex should be administered with caution to ambulatory patients who should be warned to avoid such hazards.

Use in Narcotic-Dependent Patients: Because of the narcotic antagonist activity of Buprenex, use in the physically dependent individual may result in withdrawal effects.

PRECAUTIONS:
General: Buprenex should be administered with caution in the elderly, debilitated patients, in children and those with severe impairment of hepatic, pulmonary, or renal function; myxedema or hypothyroidism; adrenal cortical insufficiency (e.g., Addison's disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis.

Because Buprenex is metabolized by the liver, the activity of Buprenex may be increased and/or extended in those individuals with impaired hepatic function or those receiving other agents known to decrease hepatic clearance.

Buprenex has been shown to increase intracholedochal pressure to a similar degree as other opioid analgesics, and thus should be administered with caution to patients with dysfunction of the biliary tract.

Information for Patients: The effects of Buprenex, particularly drowsiness, may be potentiated by other centrally acting agents such as alcohol or benzodiazepines. It is particularly important that in these circumstances patients must not drive or operate machinery. Buprenex has some pharmacologic effects similar to morphine which in susceptible patients may lead to self-administration of the drug when pain no longer exists. Patients must not exceed the dosage of Buprenex prescribed by their physician. Patients should be urged to consult their physician if other prescription medications are currently being used or are prescribed for future use.

Drug Interactions: Drug interactions common to other potent opioid analgesics also may occur with Buprenex. Particular care should be taken when Buprenex is used in combination with central nervous system depressant drugs (see WARNINGS). Although specific information is not presently available, caution should be exercised when Buprenex is used in combination with MAO inhibitors. There have been reports of respiratory and cardiovascular collapse in patients who received therapeutic doses of diazepam and Buprenex. A suspected interaction between Buprenex and phenprocoumon resulting in purpura has been reported.

CYP3A4 Inhibitors: Since the metabolism of buprenorphine is mediated by the CYP3A4 isozyme, coadministration of drugs that inhibit CYP3A4 activity may cause decreased clearance of buprenorphine. Thus patients coadministered with inhibitors of CYP3A4 such as macrolide antibiotics (e.g., erythromycin), azole antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritanovir) while receiving Buprenex should be carefully monitored and dosage adjustment made if warranted.

CYP3A4 Inducers: Cytochrome P450 inducers, such as rifampin, carbamazepine, and phenytoin, induce metabolism and as such may cause increased clearance of buprenorphine. Caution is advised when administering Buprenex to patients receiving these medications and if necessary dose adjustments should be considered

Carcinogenesis, Mutagenesis and Impairment of Fertility:
Carcinogenesis: Carcinogenicity studies were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet at doses of 0.6, 5.5, and 56 mg/kg/day for 27 months in rats. These doses were approximately equivalent to 5.7, 52 and 534 times the recommended human dose (1.2 mg) on a mg/m^2 body surface area basis. Statistically significant dose-related increases in testicular interstitial (Leydig's) cell tumors occurred, according to the trend test adjusted for survival. Pair-wise comparison of the high dose against control failed to show statistical significance. In the mouse study, buprenorphine was administered in the diet at doses of 8, 50, and 100 mg/kg/day for 86 weeks.

#189047

The high dose was approximately equivalent to 477 times the recommended human dose (1.2 mg) on a mg/m^2 basis. Buprenorphine was not carcinogenic in mice.

Mutagenesis: Buprenorphine was studied in a series of tests. Results were negative in Chinese hamster bone marrow and spermatogonia cells, and negative in mouse lymphoma L5178Y assay. Results were equivocal in the Ames test: negative in studies in two laboratories, but positive in frame shift mutation at high dose (5 mg/plate) in a third study.

Impairment of Fertility: Reproduction studies of buprenorphine in rats demonstrated no evidence of impaired fertility at daily oral doses up to 80mg/kg (approximately 763 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis) or up to 5mg/kg I.M. or S.C. (approximately 48 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis)

Pregnancy: Pregnancy Category C.
Teratogenic effects: Buprenorphine was not teratogenic in rats or rabbits after I.M. or S.C. doses up to 5 mg/kg/day (approximately 48 and 95 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis), I.V. doses up to 0.8 mg/kg/day (approximately 8 times and 15 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis), or oral doses up to 160 mg/kg/day in rats (approximately 1525 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis) and 25 mg/kg/day in rabbits (approximately 475 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis). Significant increases in skeletal abnormalities (e.g. extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after S.C. administration of 1 mg/kg/day and up (approximately 9.5 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis) and in rabbits after I.M. administration of 5 mg/kg/day (approximately 95 times the recommended human daily dose of 1.2 mg on a mg/m^2 basis), but these increases were not statistically significant. Increases in skeletal abnormalities after oral administration were not observed in rats, and increases in rabbits (1-25 mg/kg/day) were not statistically significant.

There are no adequate and well-controlled studies in pregnant women. Buprenex should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The safety of Buprenex given during labor and delivery has not been established.

Nursing Mothers: An apparent lack of milk production during general reproduction studies with buprenorphine in rats caused decreased viability and lactation indices. Use of high doses of sublingual buprenorphine in pregnant women showed that buprenorphine passes into the mother's milk. Breast-feeding is therefore not advised in nursing mothers treated with Buprenex.

Pediatric Use: The safety and effectiveness of Buprenex have been established for children between 2 and 12 years of age. Use of Buprenex in children is supported by evidence from adequate and well controlled trials of Buprenex in adults, with additional data from studies of 960 children ranging in age from 9 months to 18 years of age. Data is available from a pharmacokinetic study, several controlled clinical trials, and several large post-marketing studies and case series. The available information provides reasonable evidence that Buprenex may be used safely in children ranging from 2-12 years of age, and that it is of similar effectiveness in children as in adults.

ADVERSE REACTIONS: The most frequent side effect in clinical studies involving 1,133 patients was sedation which occurred in approximately two-thirds of the patients. Although sedated, these patients could easily be aroused to an alert state.

Other less frequent adverse reactions occurring in 5-10% of the patients were:

Nausea	Dizziness/Vertigo

Occurring in 1-5% of the patients:

Sweating	Headache
Hypotension	Nausea/Vomiting
Vomiting	Hypoventilation
Miosis	

The following adverse reactions were reported to have occurred in less than 1% of the patients:

CNS Effect: confusion, blurred vision, euphoria, weakness/fatigue, dry mouth, nervousness, depression, slurred speech, paresthesia.

Cardiovascular: hypertension, tachycardia, bradycardia.

GastroIntestinal: constipation.

Respiratory: dyspnea, cyanosis.

Dermatological: pruritus.

Ophthalmological: diplopia, visual abnormalities.

Miscellaneous: injection site reaction, urinary retention, dreaming, flushing/warmth, chills/cold, tinnitus, conjunctivitis, Wenckebach block, and psychosis.

Other effects observed infrequently include malaise, hallucinations, depersonalization, coma, dyspepsia, flatulence, apnea, rash, amblyopia, tremor, and pallor.

The following reactions have been reported to occur rarely: loss of appetite, dysphoria/agitation, diarrhea, urticaria, and convulsions/lack of muscle coordination.

In the United Kingdom, buprenorphine hydrochloride was made available under monitored release regulation during the first year of sale, and yielded data from 1,700 physicians on 3,120 patients (17,120 administrations). Data on 240 children under the age of 18 years were included in this monitored release program. No important new adverse effects attributable to buprenorphine hydrochloride were observed.

DRUG ABUSE AND DEPENDENCE: Buprenorphine hydrochloride is a partial agonist of the morphine type; i.e., it has certain opioid properties which may lead to psychic dependence of the morphine type due to an opiate-like euphoric component of the drug. Direct dependence studies have shown little physical dependence upon withdrawal of the drug. However, caution should be used in prescribing to individuals who are known to be drug abusers or ex-narcotic addicts. The drug may not substitute in acutely dependent narcotic addicts due to its antagonist component and may induce withdrawal symptoms.

OVERDOSAGE:

Manifestations: Clinical experience with Buprenex overdosage has been insufficient to define the signs of this condition at this time. Although the antagonist activity of buprenorphine may become manifest at doses somewhat above the recommended therapeutic range, doses in the recommended therapeutic range may produce clinically significant respiratory depression in certain circumstances. (See WARNINGS.)

Treatment: The respiratory and cardiac status of the patients should be monitored carefully. Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Doxapram, a respiratory stimulant, may be used. **NALOXONE MAY NOT BE EFFECTIVE IN REVERSING THE RESPIRATORY DEPRESSION PRODUCED BY BUPRENEX. THEREFORE, AS WITH OTHER POTENT OPIOIDS, THE PRIMARY MANAGEMENT OF OVERDOSE SHOULD BE THE REESTABLISHMENT OF ADEQUATE VENTILATION WITH MECHANICAL ASSISTANCE OF RESPIRATION, IF REQUIRED.**

DOSAGE AND ADMINISTRATION: Adults: The usual dosage for persons 13 years of age and over is 1 ml Buprenex (0.3 mg buprenorphine) given by deep intramuscular or slow (over at least 2 minutes) intravenous injection at up to 6-hour intervals, as needed. Repeat once (up to 0.3 mg) if required, 30 to 60 minutes after initial dosage, giving consideration to previous dose pharmacokinetics, and thereafter only as needed. In high-risk patients (e.g., elderly, debilitated, presence of respiratory disease, etc.) and/or in patients where other CNS depressants are present, such as in the immediate postoperative period, the dose should be reduced by approximately one-half. Extra caution should be exercised with the intravenous route of administration, particularly with the initial dose.

Occasionally, it may be necessary to administer single doses of up to 0.6 mg to adults depending on the severity of the pain and the response of the patient. This dose should only be given I.M. and only to adult patients who are not in a high risk category (see WARNINGS and PRECAUTIONS). At this time, there are insufficient data to recommend single doses greater than 0.6 mg for long-term use.

Children: Buprenex has been used in children 2-12 years of age at doses between 2-6 micrograms/kg of body weight given every 4-6 hours. There is insufficient experience to recommend a dose in infants below the age of two years, single doses greater than 6 micrograms/kg of body weight, or the use of a repeat or second dose at 30-60 minutes (such as is used in adults). Since there is some evidence that not all children clear buprenorphine faster than adults, fixed interval or "round-the-clock" dosing should not be undertaken until the proper inter-dose interval has been established by clinical observation of the child. Physicians should recognize that, as with adults, some pediatric patients may not need to be remedicated for 6-8 hours.

Safety and Handling: Buprenex is supplied in sealed ampules and poses no known environmental risk to health care providers. Accidental dermal exposure should be treated by removal of any contaminated clothing and rinsing the affected area with water.

Buprenex is a potent narcotic, and like all drugs of this class has been associated with abuse and dependence among health care providers. To control the risk of diversion, it is recommended that measures appropriate to the health care setting be taken to provide rigid accounting, control of wastage, and restriction of access.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED: Buprenex (buprenorphine hydrochloride) is supplied in clear glass snap-ampules of 1 ml (0.3 mg buprenorphine).

NDC 12496-0757-1

Avoid excessive heat (over 104°F or 40°C). Protect from prolonged exposure to light.

Manufactured by:
Reckitt Benckiser Healthcare (UK) Ltd.,
Hull, England, HU8 7DS

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